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Current Opinion in Genetics & Development

Mutant onco-proteins as drug targets: successes, failures, and future prospects

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Mutant onco-proteins play a direct, causal role in cancer and are therefore considered attractive drug targets. Clinical experience has supported this view, with some exceptions.However, clinical benefit has often been restricted by rapid emergence of drug-resistant clones through several distinct mechanisms. This problem can, in principle, be addressed through cocktails containing several drugs. However, the number of tumors whose survival is dependent on a single, druggable mutant onco-protein is currently unknown. The majority of tumors may be driven either by single drivers that are un-druggable, or by combinations of drivers. In both cases, new approaches will be necessary. Development of systemic RNA interference may be a solution to these problems.

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Current Opinion in Genetics & Development 2011, **21**:29–33

This review comes from a themed issue on
Genetic and cellular mechanisms of oncogenesis
Edited by Chris Marshall and Karen Vousden

Available online 12th January 2011

0959-437X/$ – see front matter

DOI 10.1016/j.gde.2010.12.002

The hypothesis that mutant onco-proteins would be effective drug targets has been a central pillar of cancer biology and drug discovery since the first mutant proteins were identified in human cancers 30 years ago. The search for novel mutant proteins is actively underway through cancer genome sequencing efforts worldwide, driven, in part by the successful exploitation of known mutant onco-proteins as drug targets. In parallel, clinical experience with drugs targeting mutant proteins is being accumulated, and we are now in a position to ask whether this approach is really justified, and how the future may unfold. Clearly, small molecules that target mutant proteins are not the only class of compound that have been intensely studied and tested: humanized monoclonal antibodies that attack proteins expressed on the surface of cancer cells (e.g. trastuzamab, rituximab and cetuximab) have been the most successful new-age cancer drugs so far. Therapies that target angiogenic factors (such as sutent, sorafenib, and bevacizumab) have also been successful, and small molecules that target amplified or hyperactive wild-type proteins have shown clinical benefit (e.g. lapatanib for HER2NEU-positive breast cancer). However, the promise of targeting mutant proteins that drive cancer is fuelling considerable efforts in discovery and drug development, and will be the subject of this discussion.

So far, so good

The number of conclusive studies and successful new drugs is small, but so far this approach has been remarkably successful, perhaps more so than could have been expected. Tumors are often unexpectedly 'addicted' to onco-proteins for survival, and reciprocally, normal cells have been relatively indifferent to the inhibition of their normal counterparts.

One of the first successful therapies based on a mutant onco-protein was for the PML-RARa protein formed by the reciprocal t(15;17)(q22;q12) translocation in 95% of acute promyelocytic leukemias [1]. All-trans-retinoic acid is effective in this disease: over 70% of newly diagnosed APL achieve long-term remission and can be considered cured. Many patients progress, however, and no longer respond to all-trans-retinoic acid therapy. Likewise, treatment of chronic myelogenous leukemia with imatinib and (later) desatanib has radically changed the clinical course of this disease, and remains the most striking examples of therapy targeted against a mutant onco-protein. Luckily, blocking the c-abl proto-oncogene kinase activity in normal cells does not cause intolerable side effects, despite early warning signs from knock-out mice that c-abl is essential for normal development [2]. Furthermore, late-stage blast crisis CML cells often remain addicted to the BCR-ABL protein, despite multiple additional mutations and gene re-arrangements. This contrasts with the view that early-stage CML responds more effectively than late-stage CML because earlier stages are driven by a single oncogene, against a relatively simple genetic landscape. Clinical responses are less durable at later stages because of the high number of leukemic progenitor cells, and, as a result, the high number of cells that express drug-resistant BCR-ABL variants [3]. Treatment of other hematopoietic malignancies by targeting mutant onco-proteins has been less successful: activating mutations in the fms-like tyrosine kinase 3 receptor FLT3 can be detected in approximately 30% of acute myeloid leukemias (AMLs) and are associated with a distinctly poor clinical outcomes. Flt3

inhibitors for AML have shown signs of modest responses, but these have not been durable, because of rapid emergence of drug resistance in most cases [4]. For other targets, such as PI 3′ kinase, Akt, and Jak2, it is too early to tell whether inhibition is safe and leads to clear clinical benefit.

The rapid development of imatinib for CML facilitated testing its effects in solid tumors, since it is active against c-kit. Gastrointestinal stromal tumors (GISTs) with c-kit mutations (85% cases) responded dramatically, but often progress through outgrowth of drug-resistant clones. These can be treated with a second targeted therapy, sunitinib [5]. These results were highly encouraging, as they suggested that targeting mutant onco-proteins might be effective in solid tumors as well as hematopoietic malignancies, with the caveat that GISTs are not of epithelial origin. Equally encouraging, but with the same caveat, imatanib appeared effective in treating c-kit-mutant melanoma [6].

The promise of treating epithelial tumors by targeting onco-proteins has been borne out through successes in nonsmall cell lung cancer. Tarceva, a potent inhibitor of EGF-receptor was approved for this disease based on overall improved survival, but it is now clear that patients with activating mutations in this receptor respond most dramatically. Indeed, the existence of mutant EGF-R genes in lung cancer was inferred from clinical responses of this subset [7–9]. However, patients often progress through emergence of second-site mutations in the EGF-R gene, and these tumor cells remain addicted to the EGF-R signaling for their survival. While overall survival is therefore disappointing, it appears likely that cocktails of two or more drugs could actually prevent recurrence through drug-resistant clones [10]. More recently, equally dramatic responses were reported following the inhibition of EML4–ALK fusion proteins characteristic of a distinct subset of nonsmall cell lung cancers [11].

With these successes, expectations were high that similar results might be seen through targeting activated BRAF in malignant melanomas, as well thyroid cancers and colorectal mutations harboring these mutations. Sorafenib, which is type II kinase inhibitor (it interacts with the inactive configuration of the kinase domain), is active against CRAF, but less so against BRAF and even less potent against the common activating allele, V600E BRAF. This drug was already in clinical trials for other indications when mutant BRAF was first identified in malignant melanoma [12], and it was quickly tested in this indication, without success, however. The rapid development of PLX 4032, which, in contrast, targets V600E BRAF effectively [13,14], appears on track for FDA approval, based on spectacular clinical responses in V600E BRAF melanoma, although the duration of these responses has been disappointing, for reasons that are not yet clear [15••].

These first generation targets were chosen with a high degree of confidence that they played a major role in causing and maintaining the disease, based on their excellent pedigrees, either as oncogenes in transforming retroviruses (e.g. ERB-B, KIT, ABL, AKT, and RAF), or their ability to transform NIH 3T3 cells in culture (e.g. ERB2/HER2/NEU), and related classical methods. Detection of activated alleles in human cancers made them compelling targets.

More recently, a target based on another pathway has been targeted in the clinic, with similar successes and failures. The hedgehog signaling pathway is vital in early development, but then becomes dormant in most cells, except in some tumors, in which the pathway is activated through mutations in the smoothened (*smo*) gene. These mutant proteins represent a different type of oncogene to those on the RAS–MAPK pathway. However, blocking the pathway in tumors with *smo* mutations appears an effective strategy [16]. These examples, though limited (*n* of one), suggest that mutant onco-proteins in other pathways might also yield drug targets, even though they lack the pedigree and familiarity derived from classical onco-proteins.

So far, most drugs that target mutant onco-proteins have been remarkably successful initially, but generally fail through the emergence of drug resistance, as discussed. Attempts to target onco-proteins indirectly, through attacking downstream enzymes, have been less successful, for different reasons. One relates to the dynamic nature of signaling networks and the consequences of disrupting feedback loops. We (and others) have referred to this problem as the 'whack-a-mole' problem: blocking one target leads to the activation of another. This effect was observed in patients treated with mTOR inhibitors, which resulted in the activation of the upstream PI 3′ kinase pathway, measured by the activation of Akt [17,18]. Likewise, we observed that MEK inhibitors can lead to hyperactivation of the upstream EGF-receptor, again measured by increased Akt phosphorylation [19] (Figure 1). In both cases, combinations of drugs may solve the problem, though the concern remains that other moles may appear when the network is suppressed effectively.

Future prospects: new targets

The newest approach for finding new targets is the reverse of the old: somatic mutations are detected in tumor DNA, and their relevance is estimated by statistical parameters, such as the frequency of mutation across multiple tumors and the nature of the somatic mutation itself [20]. These methods separate driver mutations from passengers, with caveats [21]. For example, the high frequency of mutations in KRAS reflects, in part, the large number of point mutations (codons 12, 13, 59, 61, 117 and 146) that can lead to its activation, as well as its power as an oncogenic driver.